REMARKS

The present invention relates in part to the use of affinity tags in recombinant fusion protein constructs. In particular, the claimed invention relates to affinity tags which comprise two or more modules capable of mediating binding to streptavidin.

Claims 1–34, 36, 37, 40–45 and 47-51 are pending in the application, with claims 16, 17, 32–34, 36, 37, 40–45, and 47-51 under examination. The balance of the claims has been withdrawn from examination by the Examiner in accordance with a restriction requirement.

Reconsideration of the claimed invention is respectfully requested in view of the remarks contained herein.

I. Rejection Under 35 U.S.C. §112, First Paragraph

The rejection of claims 16, 17, 32-34, 36, 37, 40-45, and 47-51 as allegedly failing to satisfy the written description requirement is respectfully traversed.

The claimed invention relates to provision of a fusion protein comprising a streptavidin–binding peptide linked to a protein sequence of interest. As recited in claim 16, the streptavidin–binding peptide comprises a sequential arrangement of two modules with an amino acid sequence of –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine. At least one of the modules comprises a sequence –His–Pro–Gln–Phe–. The streptavidin–binding peptide is located at the carboxy terminal end or at the amino terminal end of the protein sequence to which it is fused.

The Office Action asserts on page 3 that "there is no description provided of a particular protein to know what the fusion protein will look like," and so "[a] skilled artisan cannot envision the detailed chemical structure of the fusion protein." Applicants respectfully submit that the rejection does not set forth a proper basis for rejecting the claimed invention under the written description requirement.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. See MPEP § 2163.02 (citing Ralston Purina Co. v. Far-Mar-Co., Inc., 227 USPQ 177, 179 (Fed. Cir. 1985)). An adequate written description "may be shown by any description of sufficient,

relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163(II)(3)(a) (emphasis added).

As applicants have discussed previously, the claims provide all relevant information regarding the claimed fusion proteins. The claimed fusions protein have located at the amino and/or carboxyl terminus of a protein sequence of interest a streptavidin–binding peptide, and a specific sequence is called out for the streptavidin binding portion of the streptavidin–binding peptide. These factors are the "sufficient, relevant, identifying characteristics" of the claimed invention, and the skilled artisan would readily understand that the inventor had possession of this claimed invention. As far as the remainder of the fusion protein structure, a skilled artisan that is well versed in the use of affinity tags as part of a fusion protein would readily understand that such features are not relevant to possession of the invention as claimed.

In this regard, Applicants submit herewith a declaration of Dr. Thomas Schmidt, which discusses in some detail the understanding in the art regarding the use of affinity tags as part of a fusion protein. Dr. Schmidt refers to Ford *et al., Prot. Expr. Purific.*, 2, 95–107, 1991 for a review of the field regarding fusion tags as it stood more than a decade before the filing date of the present invention. As described therein, "fusion tail systems have been developed to promote efficient recovery and purification of recombinant proteins from crude cell extracts or culture media. In these systems, a target protein is genetically engineered to contain a C- or N-terminal polypeptide tail, which provides the biochemical basis for specificity in recovery and purification." Ford *et al.*, Abstract. Such affinity tags "have been designed for fusion to virtually any target protein that can be cloned and expressed in a microbial host." Ford *et al.*, page 95, right column (emphasis added). As noted in Fig. 1 of Ford *et al.*, affinity for the binding partner of the affinity tag is provided by the affinity tag itself; the remainder of the fusion protein is largely irrelevant to this interaction. Schmidt declaration, paragraphs 5 and 6.

The binding characteristics of the fusion protein to streptavidin are determined by the structure of the affinity tag, not the polypeptide sequence of interest to which the affinity tag is linked. In contrast to this understanding in the art, the Office Action asserts that "[t]he protein partner is important since binding might not occur depending on the fragment or variant thereof." Office Action, page 11. The Office Action offers no support for this assertion, and does not explain why one skilled in the art would somehow believe that the affinity tags described in the present specification would not work in the same manner as those previously known in the art.

Applicant respectfully submits that the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. Because the written description requirement demands no more, Applicant requests that the rejection be reconsidered and withdrawn.

II. Rejection Under 35 U.S.C. §112, First Paragraph

The rejection of claims 16, 17, 32-34, 36, 37, 40-45, and 47-51 as allegedly not satisfying the enablement requirement is respectfully traversed.

Like the rejection premised on the written description requirement, the enablement rejection presented in the Office Action focuses on characteristics of the claimed fusion proteins that are irrelevant from the point of view of one skilled in the art. Specifically, the rejection is focused on the overall structure of the fusion protein, as if the ability to bind to streptavidin is somehow conveyed by the complete protein sequence. This is not the case. As noted above, the skilled artisan has been aware of the use of affinity tags at the C- and N-terminus of recombinant proteins for more than two decades. Once again, Applicant notes that the binding characteristics of the fusion protein to streptavidin are determined by the structure of the streptavidin binding tag (affinity tag), **not** by the polypeptide sequence of interest to which the affinity tag is linked. And the structure of the streptavidin binding affinity tag is plainly and unambiguously recited in the claim.

In contrast, the statements in the Office Action to the effect that "no structure is provided for said fusion protein to make the correlation between structure and function" (Office Action, page 5), and "[a] skilled artisan cannot predict that any known or unknown protein would bind to streptavidin" (Office Action, pages 5-7) appear to be made from the point of view of one who has no experience in the use of such affinity tags. Indeed, the entirety of the rejection continues in this vein, alleging that various "changes" or "mutations" can affect the function of a protein, and that this allegedly introduces "unpredictability" into the invention.

None of this discussion in the Office Action appears to understand and acknowledge the routine use of such affinity tags in the art for more than two decades. *See, e.g.*, Schmidt declaration, paragraphs 5 and 6. And nothing in the Office Action explains why one skilled in the art would expect the present affinity tags to differ in their usefulness from all other affinity tags previously known in the art.

It is well established in the patent law that a specification is presumed to be enabling. Also, as stated in MPEP § 2164.04, "it is incumbent on the Patent Office… to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning…. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." Instead of providing such evidence or reasoning, the Office Action ignores the extensive knowledge available in the art concerning affinity tags generally and the teachings of the specification concerning the claimed affinity tag structures in favor of unsupported assertions of unpredictability.

Applicant respectfully submits that, when a proper enablement standard is applied, it is apparent that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

III. REJECTION UNDER 35 U.S.C. §102(e)

The rejection of claims 16, 17 and 41 under 35 U.S.C. §102(e) as allegedly being anticipated by Skerra *et al.*, U.S. Patent No. 5,506,121 is respectfully traversed.

The claimed invention relates to provision of a fusion protein comprising a streptavidin–binding peptide linked to a protein sequence of interest. As recited in claim 16, the streptavidin–binding peptide comprises a sequential arrangement of at least two modules with an amino acid sequence of –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine. The claim further specifies that at least one of the modules comprises a sequence –His–Pro–Gln–Phe–.

By contrast, the '121 patent discloses the use of a single peptide having the sequence Trp–X–His–Pro–Gln–Phe–Y-Z as an affinity tag. The Office Action points to claims 1 and 2 of the '121 patent in support of the rejection. Office Action, page 9. Applicants note, however, that these claims do not recite the claimed sequential arrangement of modules. The Office Action also points to the following discussion in the '121 patent:

> Examples of such peptide tags are the Myc-tag (Munro & Pelham (1986) Cell 46, 291-300; Ward et al. (1989) Nature 341, 544-546), the Flag peptide (Hopp et al. (1988) Bio/Technology 6, 1204-1210), the KT3 epitope peptide (Martin et al. (1990) Cell 63,843-849; Martin et al. (1992) Science 255, 192-194), an α-tubulin epitope peptide (Skinner et al. (1991) J. Biol. Chem. 266, 14163-14166) and the

> T7 gene 10-protein peptide tag (Lutz-Freyermuth et al. (1990) Proc. Natl. Acad. Sci. USA 87, 6393-6397) which have been used successfully for the detection and in some cases also for the purification of the recombinant gene product. In addition it was found that in most of the aforementioned examples these short peptide tags, which are normally 3 to 12 amino acids long, do not interfere with the biological function of the protein and therefore do not necessarily have to be cleaved after expression.

'121 patent, column 2, lines 36-51 (emphasis added). The Office Action suggests that this section inherently anticipates the claimed invention by stating that peptide tags may be 12 residues in length. Office Action, page 11. As Dr. Schmidt states in his declaration at paragraph 7, however, the above-quoted discussion is merely a factual statement in the background section of the '121 patent about certain previously known fusion/affinity tags.

Specifically, this discussion in the '121 patent simply refers to publications disclosing the use of the following tags: the Myc tag sequence (EQKLISEEDL), which is 10 residues; the Flag tag sequence (DYKDDDDK), which is 8 residues; the KT3 tag sequence (KPPTPPPEPET), which is 11 residues; α-tubulin epitope peptide tag (EEF), which is 3 residues; and the T7 gene 10 tag (MASMTGGQQMGT), which is 12 residues. Nothing in the '121 patent, whether in this section or otherwise, discloses any fusion protein which comprises two or more modules with an amino acid sequence of –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine, and at least one of which comprises a sequence –His–Pro–Gln–Phe–, as recited in the present claims.

In order to establish a *prima facie* case of anticipation, the Examiner bears the burden of demonstrating that each and every limitation of the claimed methods is present in the cited reference. In this case, the Examiner has not met that burden. Because no *prima facie* case of anticipation has been established, Applicant requests that the rejection be reconsidered and withdrawn.

IV. REJECTION UNDER 35 U.S.C. §102(e)

The rejection of claims 16, 17, 32, and 41 under 35 U.S.C. §102(e) as allegedly being anticipated by Szostak *et al.*, U.S. Patent No. 6,841,359 is respectfully traversed.

The claimed invention relates to provision of a fusion protein comprising a streptavidin–binding peptide linked to a protein sequence of interest. As recited in claim 16, the streptavidin–binding peptide comprises a sequential arrangement of two modules with an amino acid

sequence of –His–Pro–Baa– in which Baa is selected from the group consisting of glutamine, asparagine and methionine. At least one of the modules comprises a sequence –His–Pro–Gln–Phe–.

By contrast, the '359 patent fails to disclose the use of a module comprising a sequence –His–Pro–Gln–Phe–. The Office Action points to "SEQ ID NO:25; having '-His-Pro-Gln-Phe-' moiety with a specific dissociation constant" in support of the rejection. Office Action, page 9. Applicants note, however, that SEQ ID NO: 25 contains no such '-His-Pro-Gln-Phe-' sequence.

Moreover, as discussed by Dr. Schmidt in paragraph 11 of his declaration, the '359 patent informs the artisan in column 15, lines 63-66, that the presence of two HPQ (His–Pro–Gln) motifs does not confer high affinity binding to streptavidin. And, in column 10, lines 12-24, the '359 patent states that binding to streptavidin is actually conferred by the entirety of a 38 residue peptide. Thus, claim 1 of the '359 patent refers to "[a] peptide which binds streptavidin with a dissociation constant less than 10 μM and comprises an amino acid sequence having at least 80% identity to the first 38 amino acids of SEQ ID NO:25." Given this, Applicants submit that the '359 patent plainly does not disclose the claimed fusion proteins which comprise a sequential arrangement of two specified modules.

In order to establish a *prima facie* case of anticipation, the Examiner bears the burden of demonstrating that each and every limitation of the claimed methods is present in the cited reference. In this case, the Examiner has not met that burden. Because no prima facie case of anticipation has been established, Applicant requests that the rejection be reconsidered and withdrawn.

CONCLUSION

For the reasons set forth herein, Applicant respectfully submits that claims 16, 17, 32–34, 36, 37, 41–45, and 47-51 are in condition for allowance. Applicants respectfully request that the Examiner reconsider and withdraw the grounds for rejection set forth in the Office Action.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (619) 203-3186.

Respectfully submitted,

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